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Estimation of transversely isotropic material properties from magnetic resonance elastography using the optimised virtual fields method

Renee Miller^{1,2}, Arunark Kolipaka³, Martyn P. Nash^{2,4}, and Alistair A. Young^{1,2}

¹Department of Anatomy and Medical Imaging, University of Auckland, Auckland, New Zealand

²Auckland Bioengineering Institute, University of Auckland, Auckland, New Zealand ³Department of Radiology, The Ohio State University Wexner Medical Center, Columbus, OH, USA

⁴Department of Engineering Science, University of Auckland, Auckland, New Zealand

Abstract

Magnetic resonance elastography (MRE) has been used to estimate isotropic myocardial stiffness. However, anisotropic stiffness estimates may give insight into structural changes that occur in the myocardium as a result of pathologies such as diastolic heart failure. The virtual fields method (VFM) has been proposed for estimating material stiffness from image data. This study applied the optimised VFM to identify transversely isotropic material properties from both simulated harmonic displacements in a left ventricular (LV) model with a fibre field measured from histology as well as isotropic phantom MRE data. Two material model formulations were implemented, estimating either 3 or 5 material properties. The 3-parameter formulation writes the transversely isotropic constitutive relation in a way that dissociates the bulk modulus from other parameters. Accurate identification of transversely isotropic material properties in the LV model was shown to be dependent on the loading condition applied, amount of Gaussian noise in the signal, and frequency of excitation. Parameter sensitivity values showed that shear moduli are less sensitive to noise than the other parameters. This preliminary investigation showed the feasibility and limitations of using the VFM to identify transversely isotropic material properties from MRE images of a phantom as well as simulated harmonic displacements in an LV geometry.

Keywords

inverse methods; magnetic resonance elastography; myocardial stiffness; transverse isotropy; virtual fields method

1 | INTRODUCTION

Myocardial stiffness is an important determinant of cardiac function, and significant increases in global stiffness are thought to be associated with diastolic heart failure.¹ The

Correspondence: Renee Miller, 85 Park Road, Grafton 1023, Auckland, New Zealand. renee.miller@auckland.ac.nz.

ORCID

Renee Miller <http://orcid.org/0000-0003-4387-2813>

complex mechanisms that lead to an increase in myocardial stiffness are not well understood.² Myocardium is anisotropic because of its fibrous and layered architecture³ with greatest stiffness in the fibre direction, intermediate stiffness transverse to the fibres in the plane of the layer, and least stiffness orthogonal to the layers.⁴ However, layer orientation is difficult to quantify, and many groups have therefore used transversely isotropic constitutive equations.^{5,6} Animal models of heart failure show an increase in fibrosis and loss of tissue anisotropy in the left ventricular (LV) myocardium.⁷ Patients with heart failure with preserved ejection fraction (HFPEF) present with impaired filling due to increased chamber stiffness. However, intrinsic myocardial stiffness is not widely measured clinically or in research studies because of the invasiveness of measurements. Typically, a catheter is required to record ventricular pressure boundary conditions, in order to estimate material parameters from finite element analysis of deformation information obtained from imaging.⁵ A non-invasive estimate of myocardial stiffness may therefore be useful to characterise cardiovascular disease, including HFPEF.

Magnetic resonance elastography (MRE) is a non-invasive technique to estimate stiffness of soft tissues.⁸ It is a 3-stage process in which (1) non-invasive, external actuators are used to generate acoustic distortional waves in the tissue,⁹ (2) the wave displacements are quantified using a phase contrast gradient or spin-echo MRI sequence,¹⁰ and (3) the displacement information is converted into stiffness maps using an inversion algorithm.¹¹ Magnetic resonance elastography has previously been used to investigate the “effective” stiffness of myocardium at various points in the cardiac cycle without the need for catheterisation.^{9,12–22} Most of these studies, however, assumed that the myocardium is infinite and isotropic, even though myocardium is known to have anisotropic material properties.⁴ Anisotropic properties of tissue have also been studied, primarily in skeletal muscle,^{23–27} brain tissue,^{28–31} and phantoms, which include a magnetically aligned fibrin gel, a gel with embedded spandex fibres, a polyvinyl alcohol gel made anisotropic through freeze/stretch cycling and chicken breasts^{32–36} using MRE. In these studies, either 2, 3, or 5 parameters were estimated to describe the anisotropic material properties. All five parameters can be difficult to estimate from elastography displacements since 2 of the 5 parameters depend on accurate estimation of the longitudinal (dilatational) wave speed (due to compressibility), which is on the order of 300 times greater than the shear (distortional) wave speed. Limiting the number of parameters to 2 (eg, Schmidt et al³⁷) or 3 (eg, Chatelin et al³⁶) avoids estimation of compressibility. Only 1 paper (to the author’s knowledge) has estimated all 5 independent parameters from MRE displacements.³⁰

In all anisotropic inversion methods, fibre directions were either assigned using rule-based methods or using diffusion tensor MRI (DTMRI). With the development of DTMRI to examine cardiac fibre architecture, fibre information can be used in conjunction with MRE displacements³⁸ in order to assess the patient-specific anisotropic properties of cardiac tissue. This method can then be applied to investigate the progression of HFPEF by comparing the anisotropic stiffness parameters at various points in the development of the disease in order to gain a better understanding of the structural changes that occur. This paper presents preliminary work towards the quantification of homogeneous anisotropic parameters in myocardium by integrating a patient-specific geometric model of the LV with histologically measured fibre data and MRE displacement fields.

The virtual fields method (VFM), based on the variational formulation of the equilibrium equations, is an inverse method that has previously been applied to MRE displacement data to estimate isotropic shear moduli^{39,40} in phantom data. The advantage of the VFM approach is that image data are used throughout the domain, resulting in a more direct estimation procedure compared with the traditional method of solving boundary value problems. An optimised VFM has also been implemented, which minimises the impact of Gaussian noise on the estimated shear modulus.⁴¹ In this study, the optimised method was adapted for the estimation of transversely isotropic material properties from isotropic phantom MRE data and simulated harmonic displacements in an LV canine geometry embedded with fibre orientations measured from histology. Two material model formulations were tested, estimating both 5 and 3 material parameters.

This study builds upon previous research identifying anisotropic properties of tissue from MR elastography and to our knowledge, is the first to

- Estimate all 5 independent material parameters of a transversely isotropic material from MRE and compare them to known reference values,
- Compare results from 3- and 5-parameter material model formulations,
- Apply the VFM to estimate anisotropic material properties from elastography displacement fields.

2 | METHODS

2.1 | Anisotropic optimised virtual fields method

The VFM⁴² utilises the principle of virtual work (Equation 1) in order to solve for the material properties from a set of full-field displacements (or strains).

$$-\int_V \boldsymbol{\sigma} : \boldsymbol{\epsilon}^* dV + \int_S \mathbf{T} \cdot \mathbf{u}^* dS + \int_V \mathbf{b} \cdot \mathbf{u}^* dV = \int_V \rho \mathbf{a} \cdot \mathbf{u}^* dV \quad (1)$$

$\boldsymbol{\sigma}$ is the internal stress, $\boldsymbol{\epsilon}^*$ is the virtual strain field, $\mathbf{T}$ are the boundary traction forces, $\mathbf{b}$ are the body forces, ρ is the material density, $\mathbf{a}$ is the acceleration, and $\mathbf{u}^*$ is the virtual displacement field. There are an infinite number of complex-valued virtual displacement fields that satisfy the principle of virtual work in Equation 1. In the optimised VFM, the optimal virtual displacement field is calculated numerically by finding the field that minimises an objective function while satisfying a number of prescribed constraints. To simplify the problem, the virtual displacement field was set to zero on the boundaries, eliminating the boundary traction term ($\int_S \mathbf{T} \cdot \mathbf{u}^* dS$) and providing the first constraint. Body

forces ($\mathbf{b}$) were assumed to be negligible, and the forcing frequency was assumed to be the same as the resulting displacement frequency. Thus, Equation 1 was simplified to

$$-\int_V \boldsymbol{\sigma} : \boldsymbol{\varepsilon}^* dV = \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^* dV, \quad (2)$$

where ω is the loading frequency. Therefore, Equation 2 relies on 4 quantities: the internal stress field (which depends on the unknown material parameters), density, frequency of excitation, and the resulting displacement field.

2.2 | Five-parameter constitutive model

The internal stress term was expanded to introduce terms of the symmetric elasticity matrix.

$$\begin{aligned} \int_V \boldsymbol{\sigma} : \boldsymbol{\varepsilon}^* dV = \int_V & (C_{11} \boldsymbol{\varepsilon}_{11} \boldsymbol{\varepsilon}_{11}^* + C_{22} \boldsymbol{\varepsilon}_{22} \boldsymbol{\varepsilon}_{22}^* + C_{12} \boldsymbol{\varepsilon}_{22} \boldsymbol{\varepsilon}_{11}^* + C_{12} \boldsymbol{\varepsilon}_{11} \boldsymbol{\varepsilon}_{22}^* + C_{13} \boldsymbol{\varepsilon}_{33} \boldsymbol{\varepsilon}_{11}^* \\ & + C_{13} \boldsymbol{\varepsilon}_{11} \boldsymbol{\varepsilon}_{33}^* + C_{23} \boldsymbol{\varepsilon}_{33} \boldsymbol{\varepsilon}_{22}^* + C_{23} \boldsymbol{\varepsilon}_{22} \boldsymbol{\varepsilon}_{33}^* + C_{33} \boldsymbol{\varepsilon}_{33} \boldsymbol{\varepsilon}_{33}^* + 2C_{44} \boldsymbol{\varepsilon}_{12} \boldsymbol{\varepsilon}_{12}^* + 2C_{55} \boldsymbol{\varepsilon}_{13} \boldsymbol{\varepsilon}_{13}^* + 2C_{66} \boldsymbol{\varepsilon}_{23} \boldsymbol{\varepsilon}_{23}^* \\ &) dV \end{aligned} \quad (3)$$

Using equalities for a transversely isotropic material, with the preferred direction oriented in the C_{33} direction, and a modified Voigt notation: $C_{11}=C_{22}$, $C_{12}=C_{11}-2C_{44}$, $C_{13}=C_{23}$, and $C_{55}=C_{66}$. Grouping terms with similar material constants, Equation 3 was substituted into Equation 2 to give

$$\begin{aligned} & C_{11} f_{C_{11}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^*) + C_{33} f_{C_{33}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^*) + C_{44} f_{C_{44}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^*) + C_{66} f_{C_{66}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^*) + C_{13} f_{C_{13}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^*) \quad (4) \\ & = \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^* dV, \end{aligned}$$

where the functions $f_{C_{11}}$, $f_{C_{33}}$, $f_{C_{44}}$, $f_{C_{66}}$, and $f_{C_{13}}$ are linear functions of the strain and virtual strain fields and can be written explicitly as

$$\begin{aligned}
f_{C_{11}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^*) &= \int_V (\varepsilon_{11}\varepsilon_{11}^* + \varepsilon_{22}\varepsilon_{22}^* + \varepsilon_{33}\varepsilon_{33}^* + \varepsilon_{12}\varepsilon_{12}^* + \varepsilon_{13}\varepsilon_{13}^* + \varepsilon_{23}\varepsilon_{23}^*) dV \quad (5) \\
f_{C_{33}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^*) &= \int_V \varepsilon_{33}\varepsilon_{33}^* dV \\
f_{C_{44}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^*) &= \int_V (\varepsilon_{12}\varepsilon_{12}^* - 2\varepsilon_{22}\varepsilon_{11}^* - 2\varepsilon_{11}\varepsilon_{22}^*) dV \\
f_{C_{66}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^*) &= \int_V (\varepsilon_{13}\varepsilon_{13}^* + \varepsilon_{23}\varepsilon_{23}^*) dV \\
f_{C_{13}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^*) &= \int_V (\varepsilon_{33}\varepsilon_{11}^* + \varepsilon_{33}\varepsilon_{22}^* + \varepsilon_{11}\varepsilon_{33}^* + \varepsilon_{22}\varepsilon_{33}^*) dV.
\end{aligned}$$

In the VFM, a different virtual displacement field is required to solve for each unknown material parameter. Thus, for 5 parameters, 5 separate virtual displacement fields, noted by the superscripts 1 to 5 (eg, $\mathbf{u}^{*1}$), are required to solve for the 5 unknown material parameters: C_{11} , C_{33} , C_{44} , C_{66} , and C_{13} . The resulting system of equations is

$$\begin{aligned}
& \begin{bmatrix} f_{C_{11}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*1}) & f_{C_{33}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*1}) & f_{C_{44}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*1}) & f_{C_{66}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*1}) & f_{C_{13}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*1}) \\ f_{C_{11}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*2}) & f_{C_{33}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*2}) & f_{C_{44}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*2}) & f_{C_{66}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*2}) & f_{C_{13}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*2}) \\ f_{C_{11}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*3}) & f_{C_{33}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*3}) & f_{C_{44}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*3}) & f_{C_{66}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*3}) & f_{C_{13}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*3}) \\ f_{C_{11}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*4}) & f_{C_{33}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*4}) & f_{C_{44}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*4}) & f_{C_{66}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*4}) & f_{C_{13}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*4}) \\ f_{C_{11}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*5}) & f_{C_{33}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*5}) & f_{C_{44}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*5}) & f_{C_{66}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*5}) & f_{C_{13}}(\boldsymbol{\varepsilon}, \boldsymbol{\varepsilon}^{*5}) \end{bmatrix} \begin{bmatrix} C_{11} \\ C_{33} \\ C_{44} \\ C_{66} \\ C_{13} \end{bmatrix} \\
&= \begin{bmatrix} \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*1} dV \\ \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*2} dV \\ \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*3} dV \\ \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*4} dV \\ \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*5} dV \end{bmatrix}. \quad (6)
\end{aligned}$$

Specialisation constraints, described in detail in Grédiac et al and Avril et al,^{43,44} were imposed in the optimised VFM to give a well-posed system of equations with which to solve for the unknown material parameters. For example, in the case of 5 parameters, specialisation constraints for $\mathbf{u}^{*1}$ were written such that

$$\begin{aligned}
f_{C_{11}}(\boldsymbol{\epsilon}, \boldsymbol{\epsilon}^{*1}) &= 1 \quad (7) \\
f_{C_{33}}(\boldsymbol{\epsilon}, \boldsymbol{\epsilon}^{*1}) &= 0 \\
f_{C_{44}}(\boldsymbol{\epsilon}, \boldsymbol{\epsilon}^{*1}) &= 0 \\
f_{C_{66}}(\boldsymbol{\epsilon}, \boldsymbol{\epsilon}^{*1}) &= 0 \\
f_{C_{13}}(\boldsymbol{\epsilon}, \boldsymbol{\epsilon}^{*1}) &= 0.
\end{aligned}$$

Specialisation constraints for each consecutive virtual displacement field ($\mathbf{u}^{*2}$, $\mathbf{u}^{*3}$, $\mathbf{u}^{*4}$, and $\mathbf{u}^{*5}$) were developed by exchanging the place of the one in Equation 7. With these constraints, Equation 6 was written as

$$\begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} C_{11} \\ C_{33} \\ C_{44} \\ C_{66} \\ C_{13} \end{bmatrix} = \begin{bmatrix} \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*1} dV \\ \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*2} dV \\ \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*3} dV \\ \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*4} dV \\ \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*5} dV \end{bmatrix}. \quad (8)$$

Then the resulting parameters were simply computed by evaluating each right-hand side term of Equation 8.

To numerically calculate an optimised virtual displacement field, an equation was developed that describes the variance in the estimated parameters. The optimal virtual displacement field was one that minimised the variance.⁴⁵ To write the variance in terms of each virtual displacement field, Equation 4 was rewritten, separating the raw signal ($\boldsymbol{\epsilon}$) and accompanying noise ($\boldsymbol{\epsilon}_{no}$).

$$\begin{aligned}
&C_{11}(f_{C_{11}}(\boldsymbol{\epsilon}_{no}, \boldsymbol{\epsilon}^*) + f_{C_{11}}(\boldsymbol{\epsilon}, \boldsymbol{\epsilon}^*)) + C_{33}(f_{C_{33}}(\boldsymbol{\epsilon}_{no}, \boldsymbol{\epsilon}^*) + f_{C_{33}}(\boldsymbol{\epsilon}, \boldsymbol{\epsilon}^*)) + \quad (9) \\
&C_{44}(f_{C_{44}}(\boldsymbol{\epsilon}_{no}, \boldsymbol{\epsilon}^*) + f_{C_{44}}(\boldsymbol{\epsilon}, \boldsymbol{\epsilon}^*)) + C_{66}(f_{C_{66}}(\boldsymbol{\epsilon}_{no}, \boldsymbol{\epsilon}^*) + f_{C_{66}}(\boldsymbol{\epsilon}, \boldsymbol{\epsilon}^*)) + \\
&C_{13}(f_{C_{13}}(\boldsymbol{\epsilon}_{no}, \boldsymbol{\epsilon}^*) + f_{C_{13}}(\boldsymbol{\epsilon}, \boldsymbol{\epsilon}^*)) = \int_V \rho \omega^2 \mathbf{u}_{no} \cdot \mathbf{u}^* dV + \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^* dV.
\end{aligned}$$

Noise components in the strain fields were assumed to be independent Gaussian distributions with positive standard deviations, γ . Noise in each respective strain field was

assumed to have equal variance ($\gamma_{\epsilon_{11}} = \gamma_{\epsilon_{22}} = \gamma_{\epsilon_{33}} = \gamma_{\epsilon_{12}} = \gamma_{\epsilon_{13}} = \gamma_{\epsilon_{23}}$), and it was assumed that measurements were unbiased and that noise was uncorrelated from one measurement to another. With the specialisation constraints applied to the case with noise, the difference between the estimated and reference parameters ($Q^{app} - Q$ where $Q = [C_{11}, C_{33}, C_{44}, C_{66}, C_{13}]$) was written in terms of solely the noise in the signal and the virtual strain field, ϵ^* . The superscript app indicates the approximate values of the estimated parameters.

$$Q_a^{app} - Q_a = -C_{11}f_{C_{11}}(\epsilon_{no}, \epsilon^*) - C_{33}f_{C_{33}}(\epsilon_{no}, \epsilon^*) - C_{44}f_{C_{44}}(\epsilon_{no}, \epsilon^*) - C_{66}f_{C_{66}}(\epsilon_{no}, \epsilon^*) - C_{13}f_{C_{13}}(\epsilon_{13}, \epsilon^*) + \int_V \rho \omega^2 \mathbf{u}_{no} \cdot \mathbf{u}^* dV, \quad (10)$$

where $a \in [1, 5]$. For example, $Q_1 = C_{11}$. The noise in the acceleration term ($\int_V \rho \omega^2 \mathbf{u}_{no} \cdot \mathbf{u}^* dV$) was previously shown to be negligible in MRE displacement fields.⁴⁶ Therefore, the final term of Equation 10 was omitted. The variance of an estimated parameter can be written as

$$V(Q^{app}) = E([Q^{app} - E(Q^{app})]^2), \quad (11)$$

where $E(x)$ represents the expectation of x . If it is assumed that there is no bias in the measurement, then $E(Q^{app}) = Q$, and it follows that

$$V(Q^{app}) = E([Q^{app} - Q]^2). \quad (12)$$

Substituting Equation 10 into Equation 12 resulted in the following generalised equation.

$$V(Q^{app}) = E([Q^{app} - Q]^2) = \gamma^2 (Q^{app})^T [E(N^T N)] Q^{app}, \quad (13)$$

where γ represents the uncertainty in the strain measurements and

$$N = \begin{bmatrix} f_{C_{11}}(\epsilon_{no}, \epsilon^*) \\ f_{C_{33}}(\epsilon_{no}, \epsilon^*) \\ f_{C_{44}}(\epsilon_{no}, \epsilon^*) \\ f_{C_{66}}(\epsilon_{no}, \epsilon^*) \\ f_{C_{13}}(\epsilon_{no}, \epsilon^*) \end{bmatrix}, Q^{app} = \begin{bmatrix} C_{11}^{app} \\ C_{33}^{app} \\ C_{44}^{app} \\ C_{66}^{app} \\ C_{13}^{app} \end{bmatrix}. \quad (14)$$

The minimisation matrix, $\mathbf{H}$, was written as

$$\mathbf{H} = (Q^{app})^T [E(N^T N)] Q^{app}. \quad (15)$$

Therefore, an optimal virtual field was found such that Equation 15 was minimised while adhering to the constraints. Following Avril et al,⁴⁵ the virtual displacement field vector turns out to be the saddle point of the Lagrangian:

$$\mathcal{L} = \frac{\gamma^2}{2} \mathbf{u}^* T [\mathbf{H}] \mathbf{u}^* + \Lambda^T ([\mathbf{A}] \mathbf{u}^* - \mathbf{Z}), \quad (16)$$

where $\mathbf{H}$ is the matrix of estimated shear variance to be minimised (Equation 15), $\mathbf{\Lambda}$ is a vector of Lagrangian multipliers, $\mathbf{Z}$ is a vector of right-hand side constraint values, and $\mathbf{A}$ is a matrix that included specialisation constraints (Equation 7) and boundary constraints, $\mathbf{u}^*(\Omega)=0$.

Therefore, the virtual displacement field was obtained by solving the following linear system of equations:

$$\begin{bmatrix} [\mathbf{H}] & [\mathbf{A}]^T \\ [\mathbf{A}] & [\mathbf{0}] \end{bmatrix} \begin{bmatrix} \mathbf{u}^* \\ \mathbf{\Lambda} \end{bmatrix} = \begin{bmatrix} \mathbf{0} \\ \mathbf{Z} \end{bmatrix}. \quad (17)$$

Since the parameters in Q are involved in the minimisation matrix, $\mathbf{H}$, an iterative process was implemented. An initial set of parameters Q^{app} were applied to calculate an initial $\mathbf{H}$ matrix. The resulting $\mathbf{H}$ matrix was used to estimate the material properties. This step was repeated until the maximum change in estimated parameters was less than 0.1% between 2 consecutive iterations. Additionally, a maximum number of allowable iterations was set to 30. If this value was exceeded, parameters for the given model, or region, were disregarded.

The results from the 5-parameter formulation were written in terms of 2 shear moduli (G_{12} and G_{13}), 2 Young's moduli (E_1 and E_3), and a Poisson's ratio (ν_{31}) since these parameters have relevant physical meaning (ie, stiffness in shear, stiffness in tensile stretching, and volume change). Conversely, the parameters of the elasticity matrix, C_{11} , C_{33} , and C_{13} , represent a combination of tensile stiffness and volume effects and do not have a simple physical meaning. The shear moduli, Young's moduli, and Poisson's ratio can be calculated from the compliance matrix, which is the inverse of the elasticity matrix containing C_{11} , C_{33} , etc.²⁹

2.3 | Three-parameter constitutive model

A second material model formulation, developed in Feng et al,²⁹ was used, which separates the dilatational from the deviatoric properties. The equations were derived from a hyperelastic material formulation at the reference configuration. In this study, the equations in Feng et al²⁹ were rewritten as a linear combination of 4 parameters: κ , G_{12} , G_{13} , and τ ,

where $\tau = G_{12} \cdot E_3 / E_1$ and describes the anisotropic tensile ratio, and κ is defined as the ratio of the hydrostatic stress to the unit volume change.

$$\begin{aligned} C_{11} &= \kappa + \frac{8}{9}G_{12} + \frac{4}{9}\tau & C_{33} &= \kappa - \frac{4}{9}G_{12} + \frac{16}{9}\tau \\ C_{12} &= \kappa - \frac{10}{9}G_{12} + \frac{4}{9}\tau & C_{13} &= \kappa + \frac{2}{9}G_{12} - \frac{8}{9}\tau \\ C_{44} &= G_{12} & C_{66} &= G_{13} \end{aligned} \quad (18)$$

Because of the lack of confidence in estimation of the longitudinal wavelength, and hence, κ , only G_{12} , G_{13} , and τ were estimated. Then specialisation constraints, like those in Equation 7, were applied to numerically calculate 3 optimised virtual displacement fields. With these virtual displacement fields ($\mathbf{u}^{*1}$, $\mathbf{u}^{*2}$, $\mathbf{u}^{*3}$) and corresponding strain fields ($\mathbf{e}^{*1}$, $\mathbf{e}^{*2}$, $\mathbf{e}^{*3}$), the parameters were calculated as

$$G_{12} = \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*1} dV \quad G_{13} = \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*2} dV \quad \tau = \int_V \rho \omega^2 \mathbf{u} \cdot \mathbf{u}^{*3} dV. \quad (19)$$

Again, an iterative optimised virtual fields method was used to minimise the impact of noise on the estimated parameters.⁴⁴ Results from the three-parameter formulation were reported in terms of G_{12} , G_{13} , and τ . Since κ was not estimated, parameters of the elasticity matrix (eg, C_{11}) were not calculated. Therefore, only values of G_{12} and G_{13} are directly comparable between the 2 material model formulations.

2.4 | Parameter sensitivity

Equation 13 can be rewritten to clearly show that the variance in the estimated parameter is proportional to the error in the measured strain field:

$$V(Q_a) = \gamma^2 \eta_a^2. \quad (20)$$

If the variance, $V(Q_a)$, is understood as the uncertainty of the method in estimating a given parameter and γ is the uncertainty in the strain measurements, then η_a is the sensitivity of the estimated parameters to noise in the measurements. In this study, parameter sensitivity values were normalised by their respective estimated parameters (eg, η/C_{11}), which allows for the direct comparison of parameter sensitivity values within each material model formulation. However, since η_a includes the estimated parameters (see the right-hand side of Equation 13), normalisation does not allow for the direct comparison of sensitivity values between the 2 material model formulations (eg, between η/C_{11} and η/τ).

2.5 | Isotropic phantom MRE

The 2 transversely isotropic inversion methods were tested with MRE images collected from an isotropic phantom. Performing the inversion on an isotropic phantom provides a form of

validation since shear moduli and (separately) the 2 Young's moduli should be equal (ie, $G_{12}=G_{13}$ and $E_1=E_3$).

Magnetic resonance elastography images of a polyvinyl chloride cylindrical gel phantom were obtained using a 3T MR scanner (Tim Trio, Siemens Health care, Erlangen, Germany) with gradients of 27 mT/m (2.7 G/cm) and a slew rate of 163 μ s/(TE/TR = 21.27/25 ms). A pneumatic driver system (Resoundant Inc, Rochester, Minnesota) was used to apply a harmonic load to the bottom surface of the phantom at 60 Hz. Phase contrast images (native resolution = 128×63 voxels, reconstructed resolution = 256×256 voxels, slice thickness = 5 mm, FOV = 250×250 mm) were collected at 16 longitudinal locations in the midregion of the phantom. The cylindrical phantom had a radius of 76.2 mm and a height of 127 mm. At each location, 12 images were collected that encoded phase in 3 orthogonal directions at 4 phase offsets relative to the induced harmonic motion. A discrete Fourier transform was used to fit a sinusoid to the 4 phase offsets (Figure 1) at each pixel in each direction.

A finite element (FE) mesh, consisting of 30 954 nodes and 28 280 first-order hexahedral elements, was developed to represent the geometry of the imaged portion of the cylindrical phantom. Image data, which had a higher in plane resolution than the FE model, were interpolated at FE nodes using cubic-spline interpolation. Since the phantom was isotropic, 2 different arbitrary material orientations were assigned, shown in Figure 2. The volume was broken up into 18 equally sized subregions, and both formulations of the transversely isotropic optimised VFM were used to analyse each subregion.

2.6 | Left ventricle simulations

Next, both material model formulations were used to estimate transversely isotropic material properties from simulated harmonic displacements in an anatomically realistic canine LV FE model embedded with fibre orientations measured from histology.³ The model contained 5490 nodes and 4320 first-order hexahedral elements. To guide future cardiac MRE studies, various loading conditions and frequencies were tested to evaluate their impact on the accuracy of parameter estimates as well as the sensitivities of the parameters to noise. Fibre orientations were embedded in the geometric FE model by interpolating nodal parameters. Reference stiffness values, shown in Table 1, were defined based on cardiac anisotropic shear moduli measured from ultrasound elastography.⁴⁷ The large ratio of the bulk modulus to the transverse shear modulus ($\kappa/G_{12} \gg 100$) demonstrates that the fast shear wave is near the incompressible limit.³⁵

The direct steady-state dynamic analysis procedure in Abaqus 6.13 (Dassault Systèmes Simulia Corp, Providence, Rhode Island) was used to simulate MRE displacements. This is a perturbation procedure in which the response of a model to an applied harmonic load is calculated about the base state.⁴⁸ Structural damping, represented as complex moduli, was applied in order to provide a means of extracting energy from the model as would be expected for biological tissue. s is the structural damping coefficient, which is the ratio of the imaginary to real component of stiffness.

A loading test was performed in which 63 different loading combinations of x, y, and/or z displacements were prescribed on the apical and anterior surfaces (Figure 3). These surfaces

were chosen since wave propagation observed in cardiac MRE experiments originates from approximately the anterior and apical surfaces of the LV. Gaussian noise was added to the real and imaginary components of displacement for 6 selected loading cases. Noise in MR images can be adequately modelled as Gaussian, given that the signal-to-noise ratio⁴⁹ is above 3. The Gaussian distribution of noise had a mean of zero and a standard deviation (σ_{noise}) computed as

$$\sigma_{noise} = 15\% \cdot \sigma_{disp}, \quad (21)$$

where σ_{disp} was the standard deviation of the ground truth displacement field. Then, for one loading condition, various frequencies were tested in order to assess the impact on parameter identification.

3 | RESULTS

3.1 | Isotropic phantom MRE

Using the 5-parameter formulation, 4 out of 18 subregions did not converge to a solution for both arbitrarily defined material orientations. In the 3-parameter formulation, 2 subregions did not converge to a solution when the fibre direction was oriented along the global z-axis (axially), and all subregions converged when the material was oriented along the global x-axis (transverse to the axis of the cylinder). Overall, the 3-parameter formulation converged in a greater number of subregions and required fewer iterations (see Table 2).

Resulting estimated moduli for all subregions that converged to a solution are shown in Figures 4 and 5. The mean shear moduli resulted in values very close to those estimated by 3 other inversion methods, including an FE model update method⁴⁸ (FEMU: 5.55 kPa), a multimodal direct inversion method⁵⁰ (MMDI: 5.45 kPa), and a directional filter with local frequency estimation method⁵¹ (DF-LFE: 5.34 kPa). Since the phantom was isotropic, the pairs of shear moduli (G_{12} and G_{13}), and Young's moduli (E_1 and E_3), were each expected to be equal. The mean estimated shear moduli, over all subregions, from the 5-parameter formulation differed by only 0.2 kPa. However, the mean estimated Young's modulus in the material orientation (E_3) was greater than that in the transverse direction (E_1) for both arbitrarily assigned material orientations. Poisson's ratios were consistently overestimated. The true value of ν_{31} should be very close to 0.5, since the polyvinyl chloride gel was approximately incompressible. In the 3-parameter formulation, the estimated values of G_{12} varied widely across the subregions when the material orientation was aligned with the global z-axis (axially), whereas G_{13} values were accurately estimated with little variance for both material orientations. Estimated values of τ were centred at the reference value but showed large variation.

Normalised parameter sensitivity values were calculated for each subregion and are plotted in Figures 6 and 7. For the 5-parameter formulation, it should be noted that the parameter sensitivities are plotted on different scales for C_{11} , C_{33} , and C_{13} in comparison with that for the shear moduli, $C_{44}(\equiv G_{12})$ and $C_{66}(\equiv G_{13})$. Shear moduli demonstrated much lower sensitivities to noise than the other parameters. Since there were no constraints on the values

of C_{11} , C_{33} , and C_{13} , these values can be negative and still result in accurate Young's moduli.

In the 3-parameter formulation, G_{12} resulted in much greater sensitivity to noise when the material was aligned with the global z-axis (axially) than when it was oriented with the global x-axis (transverse). Parameter sensitivities were small for G_{13} irrespective of the chosen material direction. This can be understood by the fact that the relative amplitude of the displacement in the global x- and y-directions was significantly less than the global z-direction displacements. The driver was placed on the bottom of the cylindrical phantom, and the largest amplitude displacements occurred in the z-direction. Therefore, when the material orientation was aligned with the global z-axis (axial direction), the estimation of the transverse shear modulus (G_{12}) was solely dependent on small-amplitude displacements in the global x- and y-directions. When the material was in the global x-direction, both shear moduli were accurately estimated with small variances. In this case, the large amplitude through-plane motion contributed to the estimation of G_{12} . The estimated values of τ showed large variance throughout the phantom. τ resulted in large sensitivity values for both material orientations. However, with the 3-parameter formulation, the mean values of the estimated shear moduli and τ were close to those estimated using the MMDI, FEMU, and DF-LFE methods.

3.2 | Left ventricle simulations

In the LV model loading test without added Gaussian noise, 8 of the 63 simulations did not converge within 30 iterations for the 3-parameter formulation. The remaining simulations converged in between 3 and 20 iterations. The simulations that did not converge were those which had zero displacements applied to the anterior face. All simulations converged within 2 or 3 iterations for the 5-parameter formulation, and the resulting mean parameters ($\pm$ one standard deviation) were $E_1 = 6.59 \pm 0.24$ kPa, $E_3 = 10.80 \pm 0.48$ kPa, $G_{12} = 1.94 \pm 0.07$ kPa, $G_{13} = 2.52 \pm 0.05$ kPa, and $\nu_{31} = 0.4999 \pm 4.4\text{e-}6$ (note reference values: $E_1 = 6.5$ kPa, $E_3 = 10.5$ kPa, $G_{12} = 1.92$ kPa, $G_{13} = 2.5$ kPa, and $\nu_{31} = 0.4999$). For the 3-parameter formulation, the resulting mean parameters ($\pm$ one standard deviation) were $G_{12} = 2.20 \pm 0.29$ kPa, $G_{13} = 2.79 \pm 0.38$ kPa, and $\tau = 3.65 \pm 0.41$ kPa (reference: $\tau = 3.11$ kPa). The 5-parameter formulation resulted in a more accurate estimation of shear moduli than the 3-parameter formulation. In the 3-parameter formulation, τ was consistently overestimated and all 3 moduli erred by up to 33%.

Normalised sensitivity values were calculated for each parameter and are shown in Figures 8 and 9. Shear parameters resulted in lower sensitivity to noise than C_{11} , C_{33} , and C_{13} . In the 3-parameter formulation, all moduli had comparable sensitivity values.

Monte Carlo simulations were run ($n = 30$) using 6 different loading configurations. Independent distributions of Gaussian noise were added to the reference displacements for each simulation. These 6 loading configurations were chosen since they resulted in either accurate parameter identification in the loading test or low cumulative sensitivity values. Figure 10 illustrates the loads applied as well as the reference displacement fields.

The number of cases that converged in less than 30 iterations, as well as the mean number of iterations ($\pm$ one standard deviation) required for convergence, is shown in Table 3. Loading cases 60 and 4 resulted in the most accurate estimation of 3- and 5-parameters (Figure 10), respectively, in the loading test without noise. However, these cases also resulted in large normalised sensitivity values for the 3-parameter formulation. The other 4 loading cases chosen (15, 22, 31, and 38, Figure 10) resulted in low cumulative sensitivity values for both methods. These 4 loading cases, with low parameter sensitivity to noise, converged in nearly all 3-parameter simulations. Therefore, for the 3-parameter formulation, there was a clear relationship between the parameter sensitivity to noise and the convergence. The 5-parameter formulation converged in between 13 and 20 simulations out of 30 for these 4 loading cases. The convergence of the 5-parameter formulation appeared to be uncorrelated with the parameter sensitivity to noise.

Results from the simulations that converged are illustrated as box plots in Figures 11 and 12. In the 5-parameter formulation, estimates of G_{12} and E_1 varied widely for 2 simulations. G_{13} was consistently estimated accurately with relatively small variance. E_3 values varied widely and were generally overestimated. Poisson's ratios were centred at the reference value ($\nu_{31} = 0.4999$) but varied by up to 40%. In the 3-parameter formulation, the resulting estimated parameters for the 4 loading cases with low sensitivity to noise resulted in estimated values with very little variance, but the means were offset from the reference values. Only loading cases 4 and 60 showed large variance in estimated values of τ .

3.2.1 | Varying Gaussian noise—Varying amounts of noise were added to the reference displacement field for one loading case (15) and parameters were estimated using the 5- and 3-parameter formulations. The percentage, which defines the ratio between the standard deviation of noise (σ_{noise}) to the standard deviation of the displacements (σ_{disp}) as shown in Equation 21, was varied between 15% and 50%. As the amount of Gaussian noise was increased, the standard deviation of estimated parameters generally increased, and the means remained the same. In the 5-parameter formulation, on average, 19 out of 30 simulations in each Monte Carlo experiment converged, and there was no trend seen between the amount of noise and the number of converged simulations. In the 3-parameter formulation, either 29 or 30 out of 30 simulations converged, which also illustrated that there was no impact of the additional noise on convergence. τ and E_3 were consistently overestimated for each amount of Gaussian noise in the 3- and 5-parameter formulations, respectively.

The coefficient of variation, calculated as $\sigma/\bar{x}$, was plotted (Figure 13) for each parameter versus the amount of Gaussian noise added to the reference displacements in order to compare the change in relative variances. Linear regressions were computed for each parameter in order to illustrate the general trend with increasing Gaussian noise.

G_{12} and G_{13} , estimated by both methods, resulted in small coefficients of variation, which only increased minimally as the amount of Gaussian noise increased. Additionally, τ also resulted in small coefficients of variation over all amounts of noise. Conversely, E_1 , E_3 , and ν_{31} had larger coefficients of variation, which increased at a greater rate as the amount of noise increased, marked by larger slopes in the linear regressions. These results, in

agreement with the parameter sensitivity values shown in Figures 8 and 9, support the definition of η as a measure of the sensitivity of the method to Gaussian noise in the signal.

3.2.2 | Frequency analysis—The experiments run to this point have all used reference displacement fields obtained by applying a harmonic displacement at 80 Hz since this frequency has previously been used with in vivo cardiac MRE experiments.^{21,22} However, more wavelengths can be obtained in the volume by increasing the frequency of excitation. To test the impact on parameter identification, a sweep of frequencies from 60 to 200 Hz was analysed, and both the 3- and 5-parameter formulations of the optimised VFM were used to estimate anisotropic material properties using the loading condition from simulation 15.

Without added Gaussian noise, the estimated values of the shear moduli and Young's moduli varied over the frequency range, but there was no clear difference in parameter estimates with increasing frequency. However, when the normalised parameter sensitivity values were plotted versus frequency (Figure 14), it was apparent that the sensitivity of C_{11} , C_{33} , and C_{13} decreased significantly for the 5-parameter formulation as the frequency of excitation increased. There was no trend in sensitivity values versus frequency in the 3-parameter formulation. However, overall sensitivity was lowest at 80 Hz. Since calculation of parameter sensitivity values includes the estimated parameters, Q^{app} (see Equation 13), normalised parameter sensitivity values cannot be directly compared between the 5- and 3-parameter formulations.

Gaussian noise was added to the reference displacements, and a Monte Carlo simulation ($n = 30$) was run for each frequency. Table 4 shows the number of simulations that converged, out of 30, as well as the mean number of iterations until convergence ($\pm$ one standard deviation). It can be seen that as the frequency increased, the number of converged simulations for the 5-parameter formulation also increased. Conversely, no simulations converged for the 3-parameter formulation at 160, 180, and 200 Hz.

Figures 15 and 16 show box plots of the resulting estimated material parameters for the 5- and 3-parameter formulations, respectively. With the 5-parameter material formulation, G_{13} was most accurately estimated and had the smallest variance at 200 Hz. However, estimated values of E_3 showed the most variation at 200 Hz. At 100 and 160 Hz, G_{12} and E_1 were underestimated. Similar to results when varying loading conditions were applied, estimated Poisson's ratios were centred at the true values yet varied widely. With the 3-parameter formulation, loading at 80 Hz resulted in the most accurate estimation of all 3 parameters: G_{12} , G_{13} , and τ . Results at 60 Hz showed the largest variance compared with resulting estimated parameters at other frequencies.

A greater number of wavelengths, induced by applying a higher excitation frequency, resulted in a lower sensitivity to noise in the 5-parameter formulation. Conversely, the 3-parameter formulation did not converge for any simulations at higher frequencies despite the fact that the sensitivity plots did not reveal any trend in parameter sensitivity values with increasing frequency. This could be due to the fact that the 3-parameter formulation does not

accurately model the wave propagation in the LV at higher frequencies, suggesting that the bulk modulus may have a greater effect on dynamic deformations at higher frequencies.

At higher frequencies, more wavelengths were present in the LV. However, mesh resolution was not altered. Therefore, there were less elements per wavelength with which to estimate material properties. Although both material parameter formulations would have been affected by low mesh resolution, the 3-parameter formulation may have been more sensitive to this. To test this, the same frequency test could be performed with a finer LV mesh. Inspecting the parameters (G_{12} , G_{13} , and τ) during the course of the 30 iterations, it was clear that the result would not have been affected by changing the maximum number of iterations (= 30). Parameters varied widely between consecutive iterations and did not appear to be convergent.

4 | DISCUSSION

In both the 5- and 3-parameter formulations of the VFM for parameter estimation applied to MRE phantom data, the mean estimated shear moduli were similar to those estimated for the same phantom using the MMDI (5.45 kPa), FEMU (5.55 kPa), and DF-LFE (5.34 kPa) methods. However, variance in estimated parameters over the subregions was dependent on the arbitrarily assigned material orientation, and subsequently, the magnitude of displacements used to calculate each parameter. All estimated values for G_{12} , G_{13} , and τ in the phantom were within physical limits and were centred around the reference values, whereas values of E_3 and ν_{31} showed large variance and were sometimes outside of physical ranges. Therefore, with the phantom data, the 3-parameter formulation gave the most accurate results. In future studies, multiple experiments will be run with varying loading conditions on the phantom in order to investigate parameter estimation with superposition of multiple displacement fields.⁵²

Implementation of the anisotropic optimised VFM with the LV model illustrated the capability of its application to cardiac MRE. The heart presents challenges such as its thin-walled geometry and complex fibre architecture. However, it was shown in this study that accurate results can be obtained given knowledge of the material orientations (from DTI, rule-based methods, or histology), the geometry from MRI images, and an appropriate loading condition.

Without Gaussian noise, the 5-parameter material model resulted in more accurate estimation of parameters over all the loading cases. If a Poisson's ratio was chosen closer to 0.5, such as 0.499999999, the 3-parameter method may have provided better results. Also, it may be a result of the complex geometry of the left ventricular model. An investigation into the impact of loading was also performed in a simple cantilever beam geometry (results not shown). In the beam results, the 3-parameter formulation resulted in more accurate parameter estimates than the 5-parameter formulation. Therefore, the thin-walled LV geometry may have an adverse impact on the estimation of τ (in the 3-parameter formulation) due to lack of wavelengths in the transmural direction.

The 5-parameter formulation only converged in between 13 and 20 (out of 30) simulations in each Monte Carlo experiment. Several alternative convergence criteria, such as only measuring change between consecutive estimated shear moduli, were also tested (data not shown). However, none of the methods tested increased the number of simulations that converged. This could be due to the fact that the optimisation matrix (Equation 15) contains each of the approximate parameters, Q^{app} . If one value in Q^{app} varies widely from iteration to iteration (eg, one that is dependent on Poisson's ratio), then all virtual displacement fields will be affected (ie, $\mathbf{u}^{*1}$, $\mathbf{u}^{*2}$, $\mathbf{u}^{*3}$, $\mathbf{u}^{*4}$, and $\mathbf{u}^{*5}$). Therefore, one future development could be to formulate the optimisation matrix, H , in a way that does not depend on C_{11}^{app} , C_{33}^{app} , and C_{13}^{app} .

Isotropic myocardial shear stiffness has previously been measured from MRE experiments, 18,20–22,53,54 and so it is assumed that sufficient wave propagation in the heart can be achieved experimentally. Additionally, it is known that the heart undergoes nonlinear deformation throughout the cardiac cycle. However, with an 80-Hz excitation frequency, it can be assumed that the myocardium is stationary since motion of the heart due to the cardiac cycle is on the order of 1 Hz. Therefore, only the small amplitude harmonic deformations are taken into account. The loading conditions applied to the LV model in this experiment do not necessarily represent the exact harmonic motion that would occur in the LV during cardiac MRE. However, the anterior and apical surfaces were chosen since, in cardiac MRE experiments, waves generally propagate from the anterior surface through the myocardium to the posterior free wall. Depending on driver placement, waves have also been observed travelling from the apex towards the base. This was an initial test of feasibility to estimate transversely isotropic properties in a realistic LV geometry with a physiological fibre field in the presence of noise.

Current methods for estimating myocardial stiffness in vivo require invasive pressure measurements to estimate hyperelastic non-linear quasi-static material parameters by matching modelled inflation to the cardiac geometry measured from MR images given the pressure loading conditions.^{5,55} Despite measuring linear elastic versus hyperelastic material properties, MR elastography provides a non-invasive means of measuring linear dynamic cardiac tissue stiffness, eliminating the need for invasive LV pressure measurements. This study shows the feasibility of non-invasively estimating linearly elastic transversely isotropic material properties from harmonic displacement fields in an LV model.

Two recent studies^{35,52} estimated transversely isotropic properties using simulated harmonic displacements. Tweten et al⁵² estimated anisotropic parameters to within 25% without added noise in a simple cubic geometry. Our study aimed to verify that similar results could be obtained in an LV geometry with complex fibre architecture. In the absence of noise, all parameters were identified to within 33% of the reference values. In this study, when Gaussian noise was added to the reference displacement fields, moduli estimated with the 3-parameter formulation in the LV model were consistently either overestimated or underestimated. One possible cause may be the limited mesh resolution in the LV model. A previous study⁴⁶ reported that the accuracy of isotropic parameter estimates using the optimised VFM is dependent on the number of elements per wavelength. Eight elements per

wavelength resulted in approximately 5% error in the estimation of an isotropic shear modulus. In some regions of the LV model, there are as few as 4 elements per wavelength, depending on the loading configuration. Additionally, any nodes on the boundary of the FE model were prescribed a virtual displacement of zero since traction forces were unknown. Thus, in the LV model, there were only 3 free nodes in the transmural direction with which to estimate the wavelength, which may not be sufficient.

It is known that both fast and slow shear waves must be present to accurately identify transversely isotropic material properties. However, with the complex fibre distribution in the LV, it may be that fast (or slow) shear waves do not exist in all regions of the myocardium for a given loading condition, which may give rise to errors in parameter estimation. One previous study used superposition of fast and slow shear waves to test anisotropic inversion methods.⁵² Similarly, further tests could be performed in which displacement fields from the 63 loading conditions in the LV model could be superimposed to estimate the transversely isotropic material properties. In vivo, however, complex and multiple loading cases may be difficult to acquire as there are limited options for passive driver placement on the chest wall. However, superposition of displacement fields may provide more accurate parameter estimates.

5 | CONCLUSIONS

The results from this study showed that the accurate identification of material parameters using MRE data interpreted with the optimised VFM is largely dependent on the loading configuration as well as the formulation of the constitutive relation. Both the 3- and 5-parameter formulations were affected differently by the waves present in the material, as is illustrated by the parameter sensitivities to noise for each loading condition. In general, the parameters C_{11} , C_{33} , and C_{13} , and subsequently E_1 , E_3 , and ν_{31} , were much more sensitive to noise than the shear moduli using the 5-parameter material formulation. This was expected since the parameters in the upper left quadrant of the elasticity matrix (C_{11} , C_{33} , and C_{13}) are dependent on accurate estimation of the longitudinal wavelength, which is much longer than the object of interest in nearly incompressible media. In the 3-parameter formulation, all 3 parameters showed relatively similar parameter sensitivities to noise. When loading conditions that resulted in low parameter sensitivity values were selected, all or nearly all simulations converged in the presence of Gaussian noise. Conversely, the 5-parameter formulation converged in just over half of the Monte Carlo runs, and convergence appeared to be less dependent on the parameter sensitivity. As frequency increased, there was a significant decrease in parameter sensitivity to noise of C_{11} , C_{33} , and C_{13} in the 5-parameter formulation. The decrease in parameter sensitivity at higher frequencies resulted in a greater number of converged runs in the Monte Carlo test with Gaussian noise.

Overall, these results show the feasibility of estimating transversely isotropic material properties from simulated harmonic displacements in the LV model as well as from MRE displacements measured from an isotropic phantom using the anisotropic optimised VFM. Unlike other inversion methods, the optimised VFM does not assume that the medium is isotropic and infinite and does not require calculation of high-order derivatives of the displacement field, compared with direct inversion methods. Additionally, the 3-parameter

formulation bypasses the need to estimate the longitudinal wavelength. In future studies, these methods will be applied to estimate in vivo anisotropic myocardial mechanical properties non-invasively, given diffusion tensor MRI as well as MRE images.

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Abbreviations

MRE	magnetic resonance elastography
VFM	virtual fields method
LV	left ventricle
HFPEF	heart failure with preserved ejection fraction

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FIGURE 1.

Magnetic resonance elastography phase contrast images of an isotropic cylindrical phantom collected at 4 phase offsets. Each image is a 2D longitudinal slice through the phantom and represents displacement in the vertical direction

FIGURE 2.

Sketches of the 2 arbitrarily assigned material orientations are shown as well as phase images with “fibre” orientations drawn on top. “Fibre” orientations are aligned with the global (A) $z: \langle 0, 0, 1 \rangle$ and (B) $x: \langle 1, 0, 0 \rangle$ directions, respectively

FIGURE 3.

Left ventricular finite element model with (A) anterior surface nodes and (B) apical surface nodes illustrating the location of applied boundary conditions, and (C) the fibre field measured from histology

FIGURE 4.

Results from all converged subregions in the isotropic phantom, using the 5-parameter formulation, for both material orientations illustrated below each graph, showing A, transverse shear moduli (G_{12}); B, fibre shear moduli (G_{13}); C, transverse Young's moduli (E_1); D, fibre Young's moduli (E_3); and E, fibre-transverse Poisson's ratio (ν_{31}). Values measured by 3 other methods (MMDI, FEMU, and DF-LFE) are shown by dotted lines

FIGURE 5.

Results from all converged subregions in the isotropic phantom, using the 3-parameter formulation, for both material orientations illustrated below each graph, showing A, transverse shear moduli (G_{12}); B, fibre shear moduli (G_{13}); and C, anisotropic tensile ratio (τ). Values measured by 3 other methods (MMDI, FEMU, and DF-LFE) are shown by dotted lines

FIGURE 6.

Resulting estimated moduli: A, C_{11} ; B, C_{33} ; C, C_{13} ; D, C_{44} ($= G_{12}$); and E, C_{66} ($= G_{13}$) plotted versus the normalised sensitivity values. Parameters measured by 3 other methods (MMDI, FEMU, and DF-LFE) are shown by dotted lines in plots D and E

FIGURE 7.

Resulting estimated moduli: A, G_{12} ; B, G_{13} ; and C, τ plotted versus the normalised sensitivity values. Parameters measured by 3 other methods (MMDI, FEMU, and DF-LFE) are shown by dotted lines

FIGURE 8.

The estimated parameters from the elasticity matrix are plotted versus their respective normalised sensitivity values (eg, η/C_{11}). Reference values are shown as red dotted lines

FIGURE 9.

The estimated parameters (G_{12} , G_{13} , and τ) are plotted versus their respective normalised sensitivity values (eg, η/G_{12}). Reference values are shown as red dotted lines

FIGURE 10.

Left ventricular models showing loading configurations and reference displacements for simulations 4, 15, 22, 31, 38, and 60 used in the Monte Carlo noise analysis. Reference displacements represent the magnitude of displacement ($\sqrt{x^2 + y^2 + z^2}$)

FIGURE 11.

Results from all converged Monte Carlo simulations, using the 5-parameter formulation, for 6 left ventricular loading cases showing A, transverse shear moduli (G_{12}); B, fibre shear moduli (G_{13}); C, transverse Young's moduli (E_1); D, fibre Young's moduli (E_3); and E, fibre-transverse Poisson's ratio (ν_{31}). The reference values are shown by red dotted lines

FIGURE 12.

Results from all converged Monte Carlo simulations, using the 3-parameter formulation, for 6 left ventricular loading cases showing A, transverse shear moduli (G_{12}); B, fibre shear moduli (G_{13}); and C, anisotropic tensile ratio (τ). The reference values are shown by red dotted lines

FIGURE 13.

Coefficients of variation of estimated parameters in the (A) 5-parameter and (B) 3-parameter formulation plotted versus amount of Gaussian noise added to the reference displacements ($N = 15\% - 50\%$)

FIGURE 14.

Normalised parameter sensitivity values are plotted versus the excitation frequency for both the (A) 5-parameter and (B) 3-parameter formulation. Note that in (A) the sensitivity values are overlapping for η/C_{11} , η/C_{33} , and η/C_{13} . Consequently, only those for η/C_{13} can be seen

FIGURE 15.

Results from all converged Monte Carlo simulations, using the 5-parameter virtual fields method, for frequencies between 60 and 200 Hz showing A, transverse shear moduli (G_{12}); B, fibre shear moduli (G_{13}); C, transverse Young's moduli (E_1); D, fibre Young's moduli (E_3); and E, fibre-transverse Poisson's ratio (ν_{31}). The reference values are shown by red dotted lines

FIGURE 16.

Results from all converged Monte Carlo simulations, using the 3-parameter virtual fields method, for frequencies between 60 and 140 Hz showing A, transverse shear moduli (G_{12}); B, fibre shear moduli (G_{13}); and C, anisotropic tensile ratio (τ). The reference values are shown by red dotted lines

TABLE 1

Reference material properties for the left ventricular finite element model

Material Property	Symbol	Reference Value
Transverse Young's moduli	$E_1 == E_2$	6.5000 kPa
Fibre Young's modulus	E_3	10.5000 kPa
Transverse shear modulus	G_{12}	1.9225 kPa
Fibre shear moduli	$G_{13} == G_{23}$	2.5000 kPa
Anisotropic tensile ratio	τ	3.1056 kPa
Transverse Poisson's ratio	ν_{12}	0.4999
Fibre Poisson's ratio	$\nu_{31} == \nu_{32}$	0.4999
Bulk modulus	κ	3.250×10^4 kPa
Structural damping coefficient	s	0.1
Density	ρ	1.0600 g/cm ³

TABLE 2

The number of subregions of the phantom that converged in less than 30 iterations for the 5- and 3-parameter formulations are shown together with the mean number of iterations for convergence ($\pm$ one standard deviation)

Material Orientation	5-Parameter Method	3-Parameter Method
<0, 0, 1>	14 (9.71 $\pm$ 6.371)	16 (9.50 $\pm$ 6.93)
<1, 0, 0>	14 (10.86 $\pm$ 6.41)	18 (5.00 $\pm$ 1.91)

Material orientation labels are illustrated in Figure 2.

TABLE 3

Number of simulations in the Monte Carlo experiment ($n = 30$) that converged for the 5- and 3-parameter formulations, as well as the mean number of iterations for convergence ($\pm$ one standard deviation)

Simulation Number	5-Parameter Formulation	3-Parameter Formulation
4	19 (9.1 ± 3.8)	5 (16.4 ± 6.1)
15	20 (9.7 ± 5.6)	30 (5.1 ± 2.9)
22	20 (12.8 ± 7.5)	29 (6.8 ± 1.3)
31	17 (8.4 ± 4.7)	30 (4.5 ± 1.0)
38	13 (12.2 ± 6.0)	29 (6.1 ± 0.7)
60	21 (10.9 ± 6.0)	5 (18.0 ± 8.1)

TABLE 4

The number of simulations in the Monte Carlo experiment ($n = 30$) that converged for the 5- and 3-parameter formulations are shown as well as the mean number of iterations for convergence ($\pm$ one standard deviation)

Frequency (Hz)	5-Parameter Method	3-Parameter Method
60	15 (13.7 ± 7.5)	27 (12.1 ± 4.5)
80	20 (9.7 ± 5.6)	30 (5.1 ± 2.9)
100	16 (11.1 ± 5.5)	30 (5.2 ± 1.7)
120	18 (9.7 ± 3.9)	20 (10.2 ± 5.3)
140	19 (9.1 ± 2.7)	26 (11.0 ± 2.9)
160	17 (8.7 ± 3.5)	0 (NA)
180	23 (11.4 ± 7.2)	0 (NA)
200	28 (10.2 ± 5.1)	0 (NA)